REVIEW ARTICLE

Kenneth Ouriel, MD, Review Section Editor

Matrix metalloproteinases in peripheral vascular disease

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Matrix metalloproteinases (MMPs) are extracellular matrix–modifying enzymes that are important in many physiologic and pathologic vascular processes. Dysregulation of MMP activity has been associated with common vascular diseases such as atherosclerotic plaque formation, abdominal aortic aneurysms, and critical limb ischemia. For this reason, MMPs have become an important focus for basic science studies and clinical investigations by vascular biology researchers. This article reviews the recent literature, summarizing our current understanding of the role of MMPs in the pathogenesis of various peripheral vascular disease states. In addition, the importance of MMPs in the future diagnosis and treatment of peripheral vascular disease is discussed. (J Vasc Surg 2007;45:849-57.)

THE PHYSIOLOGIC ROLE OF MATRIX METALLOPROTEINASES

The cellular components of blood vessels are supported and organized by a complex structure of collagens, elastins, laminins, fibronectins, and proteoglycans known as the extracellular matrix (ECM).[1] Once believed to be merely a simple, mechanical lattice between cells, the ECM is now recognized to be a dynamic structure that facilitates and even governs cellular activity.[2] Researchers in nearly every medical discipline are examining the ECM in their quest to arrest disease, with many of the most promising advances taking place in cardiovascular research.

Much of this cardiovascular research is focused on the family of ECM-remodeling enzymes collectively termed the matrix metalloproteinases (MMPs). Twenty-three MMPs have been described in humans, and although they share a high degree of homology in their structure, their functions as ECM-modifiers vary tremendously (Table). Most MMPs are secreted freely into the extracellular space immediately after synthesis as proenzymes, but some are stored within cells (eg, MMP-9 in neutrophil granules), and others are bound to cell surface membranes (eg, MT1-MMP).[3,4]

Rigorous regulation of MMP production and activity is a crucial part of ECM homeostasis. This regulation takes place primarily at the levels of gene transcription, pro-MMP activation, and endogenous inhibition. MMPs are formed as inactive proenzymes and are activated by proteolysis in the extracellular fluid, a process that is tightly regulated by other proteases and by endogenous MMP inhibitors.[3,4]

Plasma proteins (eg α-2 macroglobulin) and tissue inhibitors of metalloproteinases (TIMPs) are the primary endogenous inhibitors of MMPs, although they also serve other physiologic functions. For example, TIMP-2 inhibits MMP-2, but is also required for MT1-MMP–mediated activation of proMMP-2.[5] The vascular microenvironment provides several specific modes of MMP regulation. For example, the cyclic strain on endothelial cells created by arterial pulsation has been shown to increase expression and activity of MMP-2 and its activator, MT1-MMP.[6,7] Furthermore, emerging evidence suggests that nitric oxide inhibits gene expression of MMP-2 from endothelial cells,[8] and MMP-9 from endothelial cells and vascular smooth muscle cells.[9]

MMPs contribute to many normal and necessary physiologic processes through their modification of the ECM.[10] These processes vary widely, ranging from embryonic development, wound healing, and keratinocyte migration to the initiation of menstruation.[11-13] Inflammation accompanied by increased MMP activity also contributes to many disease processes as several MMPs are sequestered in inflammatory cells. In fact, increased inflammation and loss of MMP regulation is the hallmark of many pathologic states, including many of the disease processes treated by vascular surgeons.

MATRIX METALLOPROTEINASES IN PERIPHERAL VASCULAR DISEASE

Atherosclerosis. Atherosclerotic disease in the coronary and peripheral arterial circulation is the leading cause of morbidity and mortality in the United States.[14] Athero-

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Table. Major human matrix metalloproteinases and associated vascular pathologies

MMP	*Associated vascular pathologies*	*Major substrates*	*Alternative names*
MMP-1	AAA, atherosclerosis	Fibrillar collagens, fibronectin	Collagenase-1, interstitial collagenase
MMP-2	AAA, atherosclerosis, arterial restenosis, critical limb ischemia	Denatured collagen, fibronectin, elastin	Gelatinase A, 72kda gelatinase
MMP-3	AAA, atherosclerosis, varicose veins	Proteoglycan, procollagenase, fibronectin	Stromelysin-1
MMP-7	Atherosclerosis	Proenzymes, fibronectin, other matrix proteins	Matrilysin
MMP-8	AAA, atherosclerosis	Fibrillar collagens, fibronectin,	Collagenase-2, neutrophil collagenase
MMP-9	AAA, atherosclerosis, arterial restenosis, critical limb ischemia	Denatured collagen, fibronectin, elastin	Gelatinase B, 92dKa gelatinase
MMP-10	Atherosclerosis	Proteoglycan, procollagenase, fibronectin	Stromelysin-2
MMP-11	Atherosclerosis	Proteoglycan, procollagenase, fibronectin	Stromylysin-3
MMP-12	AAA, atherosclerosis	Elastin, fibronectin, laminin	Macrophage elastase
MMP-13	AAA, atherosclerosis	Fibrillar collagens, fibronectin	Collagenase-3
MMP-14	AAA, atherosclerosis	Collagens, proMMPs (enzyme activation)	MT1-MMP

MMP, Matrix metalloproteinase; *AAA,* abdominal aortic aneurysm.

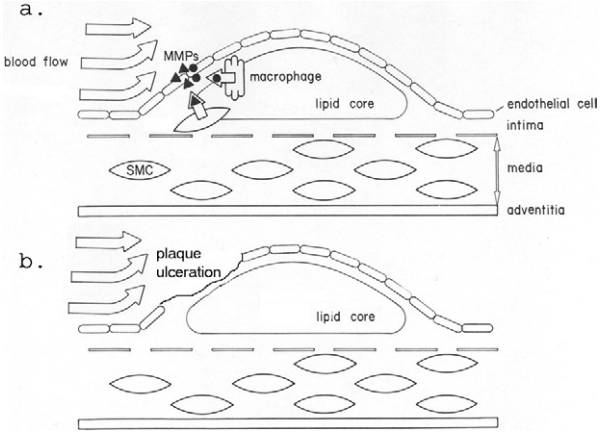

Fig 1. A, Matrix metalloproteinases *(MMP),* derived from smooth muscle cells *(SMCs)* and macrophages, degrade the atherosclerotic lesion at the "plaque shoulder" where mechanical stress is highest. **B,** This eventually results in plaque ulceration and disruption.

sclerosis is primarily an inflammatory process occurring in several distinct steps, many of which have been associated with alterations in MMP activity.[15] Specifically, MMP dysregulation is associated with leukocyte infiltration, vascular smooth muscle cell (VSMC) migration, and intraplaque matrix remodeling, each of which are key elements in atherosclerotic plaque formation.[16,17] The most intriguing investigations, however, have studied the role of MMPs in plaque instability and rupture.

Mature atherosclerotic plaques contain several sources of MMPs, most notably VSMCs (ie, MMP-2) and macrophages/foam cells (ie, MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9).[17] Loss of intraplaque MMP regulation provokes degradation of the matrix-rich fibrous cap of an atherosclerotic lesion, leading to eventual plaque disruption. This occurs primarily at the plaque "shoulders" (Fig 1), where mechanical stress caused by arterial pressure is the highest.[18]

MMP-9 is specifically associated with plaque instability in the coronary circulation.[19] An analysis of human coronary atherectomy specimens has also demonstrated higher levels of active intraplaque MMP-9 in patients with unstable angina (ie, unstable coronary plaques) compared with patients with stable angina (ie, stable coronary plaques).[20] In addition, elevated plasma MMP-9 levels in carotid endarterectomy patients are highly associated with histologic markers of unstable plaque structure as well as acute neurovascular events.[21] These studies demonstrate an association between MMP-9 and atherosclerotic plaque instability, suggesting that MMP-9 may be crucial in acute arterial insufficiency and complications caused by plaque rupture.

Clinical implications

Diagnosis. The link between plasma MMP-9 and plaque instability has led to interest in using this biomarker as a diagnostic tool, particularly in patients presenting with unstable angina and myocardial infarction. Although several studies have associated elevated plasma MMP-9 levels with acute coronary syndromes, a more rigorous correlation between MMP-9 levels and clinical status must be determined before this test can have diagnostic value.[22]

Treatment. The 3-hydroxy-3 methyl-glutaryl-coenzyme A reductase inhibitors (statins) reduce mortality at a rate that exceeds predictions based solely on the correction of hypercholesterolemia. Statins have plaque-stabilizing qualities that may be associated with an anti-MMP effect.[23] In vitro studies have shown that fluvastatin inhibits macrophage secretion of MMP-9, the MMP currently most closely linked with plaque instability.[23] Recent studies have also demonstrated statin inhibition of MMP-7, another MMP that has been linked to atherosclerotic plaque disruption.[24,25] As the MMP-inhibitory qualities of these very common medications are investigated further, the beneficial effects of statins on atherosclerosis may prove to be even more valuable and complex than previously appreciated.

ABDOMINAL AORTIC ANEURYSM

For years, atherosclerotic arterial wall damage and hypertension were believed to be the primary cause of abdominal aortic aneurysms (AAAs). The current understanding, however, characterizes AAA pathogenesis as a chronic process of inflammation, degradation, and transformation within the aortic wall, although the inducing factor remains elusive.[26]

Histologic studies of aneurysmal aortas have demonstrated specific changes in cellular content, including inflammatory cell infiltration and apoptosis of VSMCs.[27,28] Characteristic changes within the ECM of the aortic wall also occur, including a marked decrease in elastin content and an increase in collagen synthesis.[29] This decrease in the elastin/collagen ratio weakens the aortic wall, reduces its compliance, and leaves it susceptible to the mechanical stress of arterial pressure.[26] Proteolysis of elastin also results in the release of elastin degradation product, which are biologically active matrikines that have a role in chemotaxis of inflammatory cells, release of MMP-1 and MMP-2, and SMC proliferation.[30] These processes contribute to AAA development. In fact, application of an elastin degradation product to rat aortas resulted in aortic expansion and adventitial neovascularization in an experimental model.[31] MMP-2 and MMP-9 are MMPs with significant elastin-degrading activity.[32] Accordingly, alterations in the activity levels MMP-2 and MMP-9 as well as TIMP-1, the endogenous inhibitor of MMP-9, appear to have a role in AAA pathogenesis.

Matrix metalloproteinase 2. MMP-2 is constitutively expressed by VSMCs and is a key contributor to normal aortic ECM homeostasis.[26] Numerous human and animal studies have demonstrated increased MMP-2 messenger RNA (mRNA), total MMP-2 levels, and MMP-2 activity in aneurysmal aortas compared with normal and atherosclerotic aortas.[33,34] Furthermore, in contrast to wild-type mice, MMP-2 knockout (KO) mice do not form aneurysms in response to aortic injury.[35] This evidence suggests that MMP-2 contributes to AAA formation.

Matrix metalloproteinase 9. Unlike MMP-2, MMP-9 is found in negligible amounts in normal aortic tissue. MMP-9 is sequestered in neutrophils, macrophages, and other inflammatory cells. The presence of MMP-9 in aortic tissue is associated with chronic inflammation and macrophage infiltration, processes that are characteristic of AAA formation.[36] In fact, investigations have shown a correlation between elevated aortic tissue MMP-9 levels and AAAs in both humans and animal models.[37] Plasma MMP-9 levels are also elevated in patients with AAAs compared with controls.[38] Finally, MMP-9 KO mice are resistant to aneurysm formation in response to aortic injury.[39] Of interest is that these MMP-9 KO mice lose their resistance to aneurysm formation after transplantation of wild-type bone marrow capable of producing MMP-9–competent macrophages.[39] These results support the hypothesis that inflammatory cell presentation of MMP-9 is important for aneurysm formation.

In addition to its association with the initial formation of AAAs, MMP-9 has also been implicated in promoting the rupture of large, otherwise stable AAAs. Petersen et al[40] demonstrated that levels of MMP-9 were increased in ruptured aneurysms compared with intact large aneurysms.[40] These data suggest that MMP-9–mediated degradation of the aortic ECM may have a crucial role in the rupture of AAAs.

Tissue inhibitor of metalloproteinase 1. As the primary endogenous inhibitor of MMP-9, TIMP-1 may have a protective effect on AAA formation.[26] This is suggested by the fact that TIMP-1 KO mice form larger aneurysms after elastase infusion than wild-type mice.[41] Furthermore, Allaire et al[42] have demonstrated that overexpression of TIMP-1 prevents both elastin depletion and aneurysm formation and rupture in a rat model of AAA.[42] Additional studies are needed to further define the role of TIMP-1 in AAA pathogenesis.

Clinical implications

Diagnosis. The use of plasma MMP-9 levels as a screening biomarker for undiagnosed AAA has been attempted; unfortunately, normal MMP-9 levels lack the negative predictive value necessary to be used in this manner.[38] Nevertheless, plasma MMP-9 levels may be useful for monitoring patients after endovascular AAA repair (EVAR). Plasma MMP-9 levels rise sharply after open repair, most likely due to aneurysm sac manipulation, and remain elevated for ≥3 months. Patients undergoing EVAR do not demonstrate this transient elevation in plasma MMP-9 levels. Instead, the MMP-9 levels decrease gradually to well below preoperative values by 1 month after surgery if the aneurysm sac is excluded from the circulation.[43] In the presence of an endoleak, however, blood continues to circulate through the aneurysm sac, and plasma MMP-9 levels remain increased. Given the expense and risk of serial computed tomography scanning, it is plausible that serial measurement of plasma MMP levels will prove useful in the future for postoperative monitoring for endoleaks after EVAR.[43,44]

Treatment. The link between MMPs and AAAs has generated hope for a potential medical therapy. Some investigators believe that AAAs will eventually be treated primarily with medication in well-cared-for populations.[45,46] Several synthetic, broad-spectrum MMP inhibitors (eg, batimistat, marimistat) have been developed for in vivo use, although their utility in the treatment of AAA has not yet been determined.

Of interest is that doxycycline, a well known, cheap and relatively innocuous antibiotic, has generated considerable excitement as a potential treatment for AAA as well as other conditions mediated by MMPs (eg, periodontitis and arthritis). Doxycycline binds the zinc-containing active site of MMPs, nonselectively inhibiting MMP activity. It also acts to diminish cellular MMP expression.[47] Clinical trials demonstrate decreased plasma MMP-9 levels as a result of long-term administration of doxycycline.[48] Rat and mouse models exhibit inhibition of aneurysm formation after sys-

temic doxycycline administration.[39,49] A prospective clinical trial in Finland of 32 patients with small AAAs demonstrated reduced aneurysm expansion at 12 and 18 months in patients treated with doxycycline compared with placebo.[50] Finally, recent evidence suggests that local delivery of doxycycline, directly targeting the aorta without systemic administration, also reduces aortic expansion in a mouse model of AAA.[51] Local delivery of doxycycline could be accomplished in humans by using drug-eluting stent grafts, thus reducing systemic complications of doxycycline and eliminating the noncompliance associated with oral therapy. Further studies may demonstrate that doxycycline indeed has utility as a medical treatment for AAA.

In addition to doxycycline, several other medical therapies may prove useful for the treatment of AAA via inhibition of MMP activity. As already mentioned, statins have MMP-inhibitory properties.[23,25] A recent study using a mouse model of AAA showed that the administration of simvastatin reduced expression of aortic wall MMP-9, increased expression of TIMP-1, and reduced aortic expansion.[52] Not surprisingly, clinical studies show that statins reduce the rate of AAA growth during 12 and 24 months of follow-up in two series of patients.[53,54] Rapamycin, which has been shown to decrease aortic expansion and MMP-9 levels in a rat model of AAA, is another potential anti-MMP therapy that may be useful in reducing AAA expansion.[55] Finally, recent evidence indicates that inhibition of c-Jun N-terminal kinase (JNK), a proximal signaling molecule crucial for MMP-2 and MMP-9 secretion, prevents the development of AAA and even caused regression of existing AAAs in mouse models. These findings may translate into medical therapies that could utilize MMPs as a therapeutic target in the treatment of AAA.[56]

CRITICAL LIMB ISCHEMIA

After occlusion of a major artery, ischemic limbs revascularize via the distinct mechanisms of arteriogenesis and angiogenesis.[57] Arteriogenesis is the dilatation of pre-existing collateral vessels in response to changes in intravascular shear stress.[58] Angiogenesis is the de novo development of vessels from existing capillaries in response to tissue ischemia.[59] These transformations in the macrovasculature and microvasculature require changes in both the cellular and extracellular components of blood vessels and their surrounding tissues. Accordingly, investigations into the mechanisms of MMP-mediated ECM remodeling during revascularization are underway. Although limited evidence currently exists concerning the role of MMPs in arteriogenesis, significant evidence links MMP activity to the process of angiogenesis.

MMP-2 and MMP-9 have both been associated with angiogenesis. Many animal studies investigating angiogenesis in critical limb ischemia use the mouse hind limb ischemia model in which unilateral femoral artery ligation is performed.[60] The study limb of a wild-type mouse is initially profoundly ischemic after this surgery. Over the course of 28 days, however, the limb partially revascularizes, with perfusion reaching 50% to 80% of the nonischemic control limb, depending on the strain of mouse.[60] Associated with this spontaneous revascularization is a marked elevation in tissue levels of active and total MMP-2 and MMP-9 within the ischemic limb muscle.[61] In addition, MMP-9 KO mice exhibit delayed and incomplete revascularization compared to wild-type mice.[62] This indicates that MMP-9 has a specific role in the angiogenic process that can not be compensated for by MMP-2, even though both enzymes have similar substrates.

Human data on MMP activity in critical limb ischemia is limited. However, a study published in 2005 demonstrated a linear correlation between plasma MMP-9 levels and the severity of ischemia in patients with varying degrees of peripheral arterial occlusive disease (PAOD).[63]

MMPs such as MMP-2 and MMP-9 may have a role in promoting angiogenesis that goes far beyond simply degrading the ECM to allow vessels to "burrow through" and develop. In fact, ECM remodeling results in changes that contribute to the regulation of angiogenesis. MMPs release matrix-bound growth factors such as vascular endothelial growth factor (VEGF) that influence endothelial cell migration and proliferation.[64]

Interesting current evidence suggests that the ECM contains hidden signaling sites within basement membrane and interstitial matrix collagen. Monoclonal antibodies identify cryptic collagen regulatory sites HUIV26 and HU177.[65] MMP-9–dependent exposure of HUIV26 has been shown to be necessary for angiogenesis in several models.[66,67] Furthermore, studies using the mouse hind limb ischemia model demonstrate that the cryptic collagen site HU177 is exposed within ischemic muscle in a temporal fashion paralleling MMP-2 and MMP-9 activity.[61,62] This relationship between the ECM and surrounding cells is leading to further investigations designed to elucidate the role of MMPs in angiogenesis in critically ischemic limbs.

Critical limb ischemia associated with diabetes mellitus. Patients with diabetes mellitus and PAOD have a fivefold increase in the rate of amputation caused by critical limb ischemia than do patients without diabetes.[68] Diabetes mellitus alters the expression and function of MMPs, which may accelerate the progression of PAOD in affected patients. In vitro studies using a high glucose medium have demonstrated increased endothelial cell–derived MMP-1 and MMP-2 expression and activity as well as increased expression and activity of MMP-9 from monocytes.[69] Furthermore, these changes in MMP expression and activity may result in altered revascularization in response to critical limb ischemia in diabetic patients.

Indeed, a study using a hind limb ischemia model in diabetic and wild-type mice demonstrated diminished revascularization and angiogenesis in diabetic animals that was associated with increased expression of MMP-2 and markedly increased expression of MMP-12.[70] A more complete understanding of MMP function in diabetic patients will provide insight in to the complex milieu of physiologic derangements associated with diabetic vascular disease.

RESTENOSIS AFTER VASCULAR INTERVENTION

Successful endoluminal treatment of atherosclerotic lesions is limited by postintervention restenosis. Restenosis is the result of arterial remodeling that occurs by two distinct and complementary processes: intimal hyperplasia and constrictive remodeling.[71] ECM remodeling by MMPs is involved in each of these processes.

Intimal hyperplasia. Intimal hyperplasia is a thickening of the tunica intima resulting in narrowing of the vessel lumen. It occurs in several normal physiologic states, most notably during closure of the ductus arteriosus after birth[72] and is also a major cause of pathologic arterial restenosis after angioplasty and stenting procedures. The hallmark of intimal hyperplasia is VSMC migration into the intima, which reduces the luminal diameter. Degradation of the basement membrane portion of the ECM is essential for this VSMC migration, and the role of MMPs in this process is actively being expolored.[71,72]

Elevated tissue levels of MMP-2 and MMP-9 have been identified in pig models of vein bypass grafts, temporally coinciding with the period of SMC migration and neointimal formation.[73] Rats given batimastat, a generalized MMP inhibitor, demonstrated reduced neointimal formation compared with controls after Fogarty balloon–denuding injury of the common carotid artery.[74] In a separate study using a similar rat model, the nonselective MMP-inhibitor doxycycline decreased intimal hyperplasia and reduced MMP-2 and MMP-9 activity in arterial wall specimens.[75] Mice deficient for TIMP-1, the endogenous MMP-9 inhibitor, also demonstrated significantly increased neointimal formation compared with wild-type mice after periadventitial electric femoral artery injury.[76]

Specific MMP KO mice have been studied to more clearly define the role of individual MMPs in intimal hyperplasia. MMP-9 KO mice demonstrated decreased intimal hyperplasia, decreased luminal loss, and decreased VSMC migration in a carotid artery flow-cessation model of arterial remodeling.[77] A separate study using a carotid artery–denuding injury model in MMP-9 KO mice demonstrated decreased VSMC replication, VSMC migration, and arterial lesion formation compared with wild-type mice, further suggesting a role for MMP-9 in intimal hyperplasia.[78] MMP-2 KO mice also exhibit decreased intimal hyperplasia and decreased VSMC migration in a carotid artery flow-cessation model.[79] Further studies involving genetically modified mice or the development of selective in-vivo MMP inhibitors should help to elucidate further the roles of specific MMPs in intimal hyperplasia.

Constrictive remodeling. Geometric arterial remodeling results in a change in total arterial diameter, causing concentric dilatation or constriction of the lumen and arterial wall. Expansive arterial remodeling, also called compensatory enlargement or positive remodeling, is a concentric increase in luminal and total arterial diameter and was first reported by Glagov et al in 1987. This group described compensatory dilatation of coronary arteries in response to partial occlusion of the lumen by atherosclerotic plaque. This expansive remodeling is a protective compensatory mechanism that preserves luminal cross-sectional area despite significant plaque burden.[80]

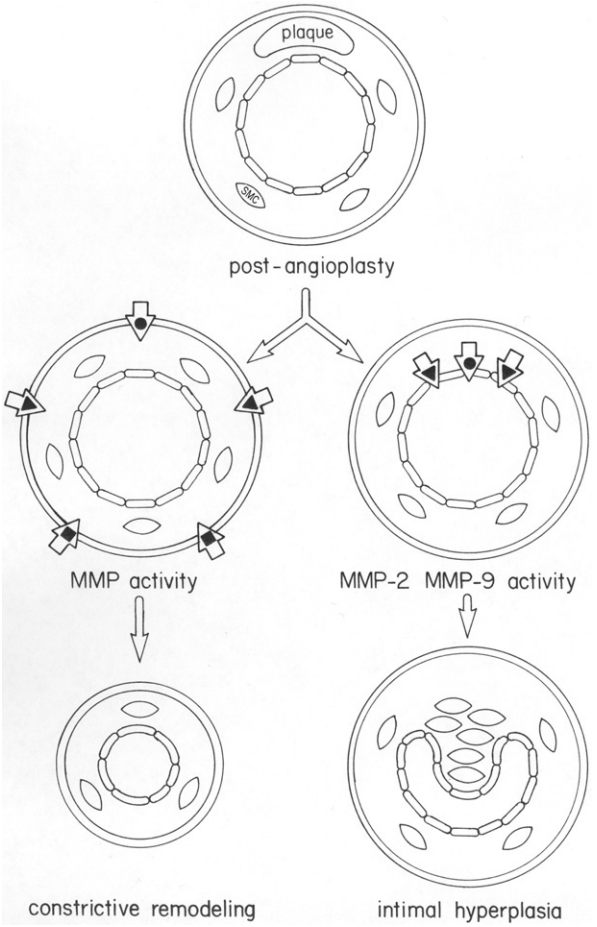

Fig 2. After angioplasty, arterial luminal narrowing occurs by the distinct processes of constrictive remodeling and intimal hyperplasia. Intimal hyperplasia is a localized process, resulting in smooth muscle cell migration into the intima and luminal narrowing. In contrast, constrictive remodeling is a diffuse, transmural process resulting in concentric reduction of the luminal and total arterial diameter. Matrix metalloproteinase *(MMP)* activity contributes to both of these pathologic processes.

In contrast, constrictive remodeling is a concentric decrease in luminal and total arterial diameter. Constrictive remodeling occurs in response to angioplasty and is a major cause of postintervention restenosis, distinct from intimal hyperplasia (Fig 2).[71] Constrictive remodeling is believed to be the result of changes in collagen and elastin metabolism mediated by alterations in MMP activity after angioplasty.[81] Angioplasty is a specific form of tissue injury, and the blood vessel wall responds accordingly by demonstrating features of wound healing such as deposition of collagen and tissue contraction. These changes, which are partly mediated by MMPs, result in arterial constriction and loss of luminal and arterial diameter.[17]

Several studies demonstrate a reduction in postangioplasty constrictive remodeling after the administration of MMP inhibitors. De Smet et al[82] reported that batimastat significantly decreased constrictive remodeling and late lumen loss after balloon angioplasty in pigs.[82] A second study using the oral MMP inhibitor marimastat in a similar pig model yielded similar results.[83] These studies suggest that MMP activity may be integral to constrictive remodeling and loss of vessel diameter after endoluminal therapy.

Therapeutic potential. Because studies in rodents and pigs suggest that postangioplasty intimal hyperplasia and constrictive remodeling may be decreased through MMP inhibition, similar studies have been attempted in higher animals and in humans. In one study, atherosclerotic monkeys were given the broad-spectrum MMP inhibitor RO113-2908 after iliac artery stenting. Of interest was that no difference in lumen diameter, intimal hyperplasia, or constrictive remodeling was identified between the study and control groups after 4 weeks.[84] Two separate human studies using drug-eluting stents containing batimastat have also been performed. The results of these human studies showed neither angiographic improvement nor a decreased requirement for endoluminal reintervention as a result of MMP inhibition.[85,86] It is unclear if these disappointing findings are the result of limitations in drug delivery, incomplete MMP inhibitory activity of the drugs, or if these studies simply demonstrate the ineffectiveness of MMP inhibition in reducing restenosis. Because the results of these primate and human studies contradict the data obtained from lower animal studies, further investigations are clearly necessary to determine if MMP inhibition has a role in the treatment of arterial restenosis by intimal hyperplasia and constrictive remodeling.

VENOUS DISEASE

Varicose veins. More than a century has passed since Trendelenberg's 1891 proposal implicating valvular incompetence in the pathogenesis of varicose vein disease. Although this model is still being taught today, the current understanding of ECM remodeling in vascular disease has sparked interest in new theories of varicose vein pathogenesis.[87] Varicose vein development may, in fact, be mechanistically similar to AAA development. Decreased vessel wall strength, alterations in ECM content, and MMP dysregulation may play a key role.[88]

Interstitial collagen III is important for the stretch resistance of the connective tissue of veins. MMP-3 may contribute to vein wall weakness and varicose vein formation via excessive degradation of collagen III. Kowalewski et al[88] have demonstrated that MMP-3 levels in varicose vein biopsy specimens are almost twice as high as those found in healthy veins.

An in vitro study by Sansilvestri-Morel et al[89] supports this finding. They showed that VSMCs cultured from varicose veins produce higher levels of MMP-3 than VSMCs from healthy veins. This study also demonstrated a reduction of collagen III in the culture media of varicose vein VSMCs. Despite this reduction in collagen III, levels of collagen III propeptide are comparable with levels found in the control VSMC cultures, indicating that collagen III is produced in both cultures in similar amounts. This finding suggests that the decreased collagen III levels in the varicose vein cultures are due to extracellular degradation, likely owing to increased MMP-3 activity rather than decreased production.[89] This evidence suggests a role for MMP-3 in varicose vein pathogenesis and is the basis for continuing investigations.

Deep vein thrombosis. Deep vein thrombosis (DVT) is a significant clinical problem that can result in devastating acute events such as pulmonary embolism. Post-thrombotic syndrome occurs in a significant percentage of patients after DVT resolution and results in pain, edema, and ulceration, yet the pathogenesis of this syndrome is unclear.[90] Several investigators propose a mechanism by which inflammation and MMP hyperactivity associated with thrombus resolution result in vein wall injury, scarring, and post-thrombotic sequelae.[91-93]

Increased MMP-9 expression is associated with the early phase of DVT resolution.[91] Recent studies by Henke et al[92] in neutropenic rats suggest that this early increase in MMP-9 is associated with neutrophil infiltration within the thrombus; moreover, increased MMP-2 transcription and activity in the vein wall is associated with the late phase of DVT resolution in experimental models.[91,93] In addition, increased levels of MT1-MMP, a membrane-bound activator of MMP-2, are associated with this increased MMP-2 expression and activity, further suggesting a role for MMP-2 in DVT pathophysiology.[93] Continued elucidation of the role of MMPs in DVT resolution and post-thrombotic vein wall changes may demonstrate that MMPs are a potential therapeutic target in preventing the long term sequelae of DVT.

Chronic venous ulcers. Successful wound repair requires a tightly coordinated proteolytic response involving multiple MMPs, including MMP-1, MMP-2, MMP-7, MMP-9, and MMP-10.[11,12] In contrast, loss of MMP regulation may be significant in the pathogenesis of chronic, nonhealing wounds such as venous ulcers.[94] Several studies have demonstrated increased MMP-2 expression and activity in chronic venous ulcers.[95-97] Furthermore, increased expression of the MMP-2 activator MT1-MMP is also found in chronic venous ulcers, further suggesting a role for MMP-2 in this disease process.[97]

The specific role of MMP2 in venous ulcer pathogenesis remains unclear, however. MMP-2 hyperactivity may inhibit wound healing via excessive basement membrane degradation leading to loss of epidermal integrity.[95] In vitro studies have demonstrated diminished angiogenesis in the presence of exudate taken from chronic venous ulcers. This decreased angiogenesis was reversed by the addition of an inhibitor of MMP-2 and MMP-9, suggesting that the MMP balance in chronic venous ulcers has an antiangiogenic effect.[98] In a bench-to-bedside effort, a recent trial examined the potential therapeutic benefit of MMP-inhibitor-impregnated dressing for the treatment

of chronic wounds with encouraging results.[99] This modality may prove useful in the treatment of venous ulcers.

CONCLUSION

MMPs continue to represent an exciting focus for basic science and clinical investigation in peripheral vascular disease. Many traditional theories of vascular pathophysiology have already been set aside in favor of newly discovered, MMP-mediated mechanisms. A new class of therapeutic agents may soon be developed that will offer patients noninvasive methods for treating vascular disease. The introduction of endovascular technology has transformed the way vascular disease is treated. It is possible that therapeutic modulation of MMP function may one day change the practice of vascular surgery even further.

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